DEVELOPMENT AND VALIDATION OF ANALYTICAL METHODS FOR THE QUANTITATION OF SOME DRUGS IN BULK AND IN PHARMACEUTICAL DOSAGE FORM

Research proposal submitted

To

Swami Ramanand Teerth Marathwada University, Nanded

For the award of degree of

Doctor of Philosophy

in the faculty of Pharmaceutical Sciences and Technology

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2016 - 2017

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1. INTRODUCTION

This chapter deals with the introductory part of the development and validation of analytical methods and literature survey. The development of analytical methods[1] plays a great role in the formulation and development of pharmaceuticals. The need to validate an analytical method is encountered by analysts in the pharmaceutical industry on an almost daily basis, because adequately validated methods are a necessity for approvable regulatory filings. These analytical methods are used by quality control laboratories to ensure the identity, purity, potency and performance of formulated drug products. The combination therapy now days are becoming more popular, and needs a special quality control check. Therefore the analysts are required to develop a new method for their analysis.

The analytical methods developed for the assessment of quality control of pharmaceutical products are always subjected to different requirements. The current good manufacturing practices (cGMP) regulation[2] requires the test methods that are used for assessing compliance of pharmaceutical product with established specification need proper accuracy and reliability. Therefore it is obligatory for the analytical chemist to adopt novel techniques that not only yield accurate and precise results but also are rapid and reproducible.

The various method developed are used in quantitative analysis[3]. Amongst these, the instrumental methods occupy important position in quantitative and qualitative analysis due to their better sensitivity and rapidity. The overwhelming demand for better sensitivity, greater resolution, and automatic recording of data has resulted in more and more sophisticated and computerized instruments using which analyst can develop accurate, rapid, sensitive, economical, specific and reproducible methods.

Recent progress in method development has been largely a result of improvements in analytical instrumentation. The instrumental methods like Ultra Violet (UV) spectrophotometry[4], Fourier Tranform Infrared (FT-IR) spectrophotometry[5], high performance liquid chromatography[6] (HPLC) and high performance thin layer chromatography[7] (HPTLC) have better acceptance due to rapid speed of analysis.

The UV spectroscopic methods[8] which usually measures the intensity of electromagnetic radiation emitted or absorbed by the drugs is of great importance in the quality control test. The careful manipulations of the experimental parameters in UV-visible spectrometer often enables the analyst to estimate one or simultaneously, more than one component present in a

mixture without their prior separation. Spectroscopic methods using hydrotropic solution[9] (Solution of urea, Sodium acetate, Sodium citrate, Sodium benzoate, etc) now a day is also used for the determination of poorly water soluble drugs.

At the start, FT-IR spectroscopy was used as a qualitative tool but in last two decades tremendous quantitative work has been published because, it is a simple, rapid and eco-friendly technique and also involves easy sample preparation with reduced or no pre-treatment steps. The diffuse reflectance infrared fourier transform (DRIFT) spectroscopy was projected to be relatively better techniques for quantitative analysis of solid-state samples. The quantitative determination of various compounds by infrared spectroscopy is based on the determination of the concentration of one of the functional groups of the compound being estimated.[10-11]

HPLC, HPTLC are the widely used chromatographic techniques in the qualitative and quantitative analysis. HPLC is the most popular chromatographic technique used for the quality control of pharmaceuticals. The reason for the popularity of this method is its sensitivity and acceptability to accurate quantitative determinations and its suitability for separating non volatile species or even thermally fragile ones. Isocratic and gradient reverse-phase high-performance liquid chromatography (HPLC) have evolved as the primary techniques for the analysis of non-volatile active pharmaceutical ingredients and impurities. Above its entire wide spread applicability to substances that are of prime interest of industry to many fields of sciences and to the society.

HPTLC is the most reliable method amongst all for the quantitation at micro, nano and even when present in complex formulations. HPTLC can simultaneously handle several samples even of divergent nature and composition. The HPTLC technique is based on in situ measurement of visible, UV-absorbance, fluorescence or fluorescence quenching directly on the layer. Since chromatographic zones re-emit a lower light intensity than environment around it, the measurements are made comparison of reflection of spot with free area around it. The scanner converts barrel into peaks and peak height or area is related to the concentration of substance on the spot.

Analytical methods development and validation play important roles in the discovery, development and manufacture of pharmaceuticals. Method development is the process of proving that an analytical method is acceptable for use to measure the concentration of an API in a specific compounded dosage form. In general terms pharmaceutical analysis

comprises of those procedures which are necessary to determine the identity, strength, quality and purity of drugs and chemicals. Analytical method validation is the corner stone of process validation. Method validation is the process to confirm that the analytical procedure employed for a specific test is suitable for its intended use. Results from method validation can be used to judge the quality, reliability and consistency of analytical results; it is an integral part of any good analytical practice. Hence there is a need to validate the developed new methods.[12]

2. VALIDATION OF METHOD

Once the method is finalized it will be validated using a series of experiments designed to challenge the method and access its suitability to measure the analytes under normal running condition. The validation protocols usually followed will be that defined by the International Conference on Harmonization (ICH) under their validation for analytical procedure methodology, for following parameters,[13]

A. Specificity
B. Linearity
C. Range
D. Accuracy
E. Precision
F. Detection limit
G. Quantitation limit
H. Robustness
I. Ruggedness
J. System suitability testing

3. STABILITY-INDICATING ASSAY METHOD

A stability-indicating method is a validated quantitative analytical procedure that can be used to detect how the stability of the drug substances and drug products changes with time. A stability-indicating method accurately measures the changes in active ingredients concentration without interference from other degradation products, impurities and excipients. The degradation studies indicated the susceptibility of drugs to various degradations. Knowledge from stability studies enables understanding of the long-term effects of environment on drugs.[14-17]

4. OBJECTIVE OF WORK

Pharmaceutical industries are manufacturing multiple drug formulations to meet the market demand. It is a well known fact that a combination of a drug has a wider range to treat ailments as compared to the single drug component. There are very few methods reported for simultaneous analysis of drug component of such multicomponent formulations. Almost all pharmacopoeial methods available for the analysis of such formulations are applicable only after prior separation of drug components, hence, making them tedious and time consuming. There is possible to be loss of accuracy and precision due to extractions and/or separation. The simultaneous analysis procedures avoid these time consuming extractions and separations leads to economical in the sense use of expensive reagents by minimizing them. Thus, developing more accurate, precise and efficient methods for simultaneous analysis of the multicomponent formulations will be rational, and it will have immediate pharmaceutical applications.

The non availability of UV, FT-IR, HPLC and HPTLC method until now for the simultaneous estimation of the combination made it worthwhile objective to perceive the present research work. It is also planned to validate the developed methods as per ICH norms.

The methodology on current research work includes use of sophisticated instruments. It is therefore proposed to perform complete stability studies of drug(s) to identify the presence of level of any degradation which will leads to maintain quality and to minimize the level of degradation in active pharmaceutical ingredients and pharmaceutical preparations. Finally, all the data will be reported in reputed journals.

Therefore in the proposed project attempts will made to develop a simple, accurate, precise and economic method(s) for single and/or simultaneous analysis of different drugs and/or combinations from below mentioned categories of drugs and to validate the developed method(s).

List of drugs categories:

Antidiabetic drugs

Cardiovascular drugs

Antiviral drugs

Antitubercular drugs

Antimalarial drugs

Non-steroidal Anti-inflammatory drugs

5. PLAN OF WORK

A. Literature Survey:

Thorough survey of literature available for listed drugs and their combinations (regarding their physical and chemical properties, pharmacology and various analytical methods) shall be conducted.

This will form the basis for the development of new UV spectrophotometric, FT-IR spectrophotometric, HPLC and HPTLC methods of analysis.

B. Procurement of Drug Sample:

Procurement of drug specimens draws utmost priority. The drugs will be procuring as gift sample from respective companies / research laboratories of those brands.

C. Duration of work:

Table 1: Year wise plan of work and targets to be achieve

Period of study	Achievable Targets
0 - 6 Months	Literature Survey, Lab setting and Procurement of Chemicals, drugs and other requirements.
6 - 12 Months	Analytical method(s) development and Validation by using various techniques like UV/FT-IR/HPLC/HPTLC methods.
12 - 18 Months	
18 - 24 Months	Forced degradation studies by chemical and physical stress testing as per ICH guidelines
24 - 30 Months	Presentation/ Publication of research work in conferences and reputed journals.
30 - 36 Months	Compiling and interpretation of the data and Report Writing and Publication.

D. Methodology:

I. Selection of analytical techniques.

a. UV Spectrophotometric method.
b. FT-IR Spectrophotometric method.
c. HPLC method
d. HPTLC method

II. Identification and preliminary study of pure drug samples.

III. Forced degradation studies.

a. Acid degradation
b. Alkali degradation

c. Neutral degradation
d. Oxidative degradation
e. Photo degradation (natural light / UV radiation)
f. Thermal degradation

IV. Compilation of data.

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